Postinfectious Cough
ACCP Evidence-Based Clinical Practice Guidelines
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Background: Patients who complain of a persistent cough lasting > 3 weeks after experiencing the acute symptoms of an upper respiratory tract infection may have a postinfectious cough. Such patients are considered to have a subacute cough because the condition lasts for no > 8 weeks. The chest radiograph findings are normal, thus ruling out pneumonia, and the cough eventually resolves, usually on its own. The purpose of this review is to present the evidence for the diagnosis and treatment of postinfectious cough, including the most virulent form caused by Bordetella pertussis infection, and make recommendations that will be useful for clinical practice.

Methods: Recommendations for this section of the guideline were obtained from data using a National Library of Medicine (PubMed) search dating back to 1950, which was performed in August 2004, of the literature published in the English language. The search was limited to human studies, using the search terms “cough,” “postinfectious cough,” “postviral cough,” “Bordetella pertussis,” “pertussis infection,” and “whooping cough.”

Results: The pathogenesis of the postinfectious cough is not known, but it is thought to be due to the extensive inflammation and disruption of upper and/or lower airway epithelial integrity. When postinfectious cough emanates from the lower airway, this is often associated with the accumulation of an excessive amount of mucus hypersecretion and/or transient airway and cough receptor hyperresponsiveness; all may contribute to the subacute cough. In these patients, the optimal treatment is not known. Except for bacterial sinusitis or early on in a B pertussis infection, therapy with antibiotics has no role, as the cause is not bacterial infection. The use of inhaled ipratropium may be helpful. Other causes of postinfectious cough are persistent inflammation of the nose and paranasal sinuses, which leads to an upper airway cough syndrome (previously referred to as postnasal drip syndrome), and gastroesophageal reflux disease, which may be a complication of the vigorous coughing. One type of postinfectious cough that is particularly virulent is that caused by B pertussis infection. When the cough is accompanied by paroxysms of coughing, posttussive vomiting, and/or an inspiratory whooping sound, the diagnosis of a B pertussis infection should be made unless another diagnosis is proven. This infection is highly contagious but responds to antibiotic coverage with an oral macrolide when administered early in the course of the disease. A safe and effective vaccine to prevent B pertussis is now available for adults as well as children. It is recommended according to CDC guidelines.

Conclusions: In patients who have a cough lasting from 3 to 8 weeks with normal chest radiograph findings, consider the diagnosis of postinfectious cough. In most patients, a specific etiologic agent will not be identified, and empiric therapy may be helpful. A high degree of suspicion for cough due to B pertussis infection will lead to earlier diagnosis, patient isolation, and antibiotic treatment. (CHEST 2006; 129:138S–146S)

Key words: Bordetella pertussis; pertussis infection; postinfectious cough; postviral cough

Abbreviations: CDC = Centers for Disease Control; FHA = filamentous hemagglutinin; PCR = polymerase chain reaction; PT = pertussis toxin; UACS = upper airway cough syndrome

Patients may complain of a persistent cough following symptoms of an upper respiratory tract infection; when the cough lasts for > 3 weeks, it is no longer considered to be an acute cough. Instead, it is considered to be in the category of subacute cough. Some authors have labeled the cough following a
viral or virus-like infection (eg, with Mycoplasma or Chlamyphila) as a postinfectious cough. In the definition of postinfectious cough are the following elements: the cough lasts no > 8 weeks; the chest radiograph findings are negative, ruling out pneumonia; and the cough eventually resolves, usually on its own. Hence, the subacute postinfectious cough is distinguished from the chronic cough by the duration of coughing, with the chronic cough lasting for at least 8 weeks and in most instances for many months and even years. Recommendations for this section of the guideline were obtained from data using a National Library of Medicine (PubMed) search dating back to 1950, which was performed in August 2004, of the literature published in the English language. The search was limited to human studies, using the search terms “cough,” “postinfectious cough,” “postviral cough,” “Bordetella pertussis,” “pertussis infection,” and “whooping cough.”

Postinfectious Cough

Pathogenesis

While the pathogenesis of the postinfectious cough is not known, it has been thought to be due to the extensive disruption of epithelial integrity and widespread airway inflammation of the upper and/or lower airways with or without transient airway hyperresponsiveness.5–8 Bronchoscopy and biopsy performed on patients with uncomplicated influenza A infection, for example, reveals extensive desquamation of epithelial cells to the level of the basement membrane.9 The percentage of lymphocytes and neutrophils in BAL fluid is high, and bronchial biopsy material shows a lymphocytic bronchitis.9 Although bronchial hyperresponsiveness is present in some patients with postinfectious cough, eosinophilic inflammation, which is typical of asthma, is absent.10 Despite the presence of symptomatic heightened coughing, cough receptor sensitivity to capsaicin and tartaric acid inhalation challenge has not been found to be heightened in the acute and convalescent phases of postinfectious cough due to Mycoplasma pneumoniae.11 On the other hand, with upper respiratory infections of undetermined cause that produce a persistent cough, it has been shown that there is an increased sensitivity to inhaled capsaicin during the acute phase of the illness. When tested during convalescence at 4 weeks and beyond, cough sensitivity returns to baseline.12

Therefore, transient inflammation of the lower airways is likely to be important in the pathogenesis in some patients with postinfectious cough. This speculation is based on the fact that cough may be induced by the heightened responsiveness of the cough receptors, by bronchial hyperresponsiveness as is seen in cough-variant asthma, or by impaired mucociliary clearance from the disruption of the epithelial lining of the airways. Because airway inflammation causes mucus hypersecretion, retained secretions resulting from excessive mucus production and decreased clearance may be another important mechanism of cough. Additionally, persistent inflammation of the upper airway, particularly the nose and paranasal sinuses, can be the cause of or can contribute to postinfectious cough. When secretions drain into the hypopharynx and larynx or when there is inflammation of the upper airway, cough receptors can be stimulated, and this may persist for weeks or longer following an upper respiratory infection.13 Another mechanism to consider in postinfectious cough is gastroesophageal reflux. Although viral infection itself does not cause gastroesophageal reflux disease, the vigorous coughing that follows may induce or aggravate preexisting reflux disease because of the high abdominal pressures that are generated. Patients with the subacute postinfectious cough are therefore similar to those with chronic cough. The pathogenesis is frequently multifactorial.14,15

Recommendations

1. When a patient complains of cough that has been present following symptoms of an acute respiratory infection for at least 3 weeks, but not more than 8 weeks, consider a diagnosis of postinfectious cough. Quality of evidence, expert opinion; net benefit, intermediate; strength of recommendation, E/B

2. In patients with subacute postinfectious cough, because there are multiple pathogenetic factors that may contribute to the cause of cough (including postviral airway inflammation with its attendant complications such as bronchial hyperresponsiveness, mucus hypersecretion and impaired mucociliary clearance, upper airway cough syndrome [UACS], asthma, and gastroesophageal reflux disease), judge which factors are most likely provoking cough before considering therapy. Quality of evidence, expert opinion; net benefit, intermediate; strength of recommendation, E/B

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Prevalence

In adults, postinfectious cough has been reported with a variable frequency. In retrospective studies of unselected patients with a history of upper respiratory tract infection, the frequency has ranged from 11 to 25%. During outbreaks of obvious infection with *M. pneumoniae* and *Bordetella pertussis*, the frequency of postinfectious cough increases to 25 to 50% in selected series. In prospective studies of unselected patients, many of whom had a history of upper respiratory tract infection, postinfectious cough was not diagnosed. The explanation for this low frequency in the latter studies is likely related to differences in the study populations reported and to the fact that most patients in these series had experienced the cough for many months or years.

In children, the specific infection causing the postinfectious cough in most cases remains unidentified. Respiratory viruses (particularly respiratory syncytial virus, influenza, parainfluenza, and adenovirus), *M. pneumoniae*, *Chlamydophila pneumoniae* strain TWAR, *Moraxella catarrhalis*, and *B. pertussis* have all been implicated. In the general population, there is an average of 2.2 viral respiratory infections per person per year, but in children this number is considerably higher. Children under 5 years of age have 3.8 to 5 infections per person per year. Those children in daycare are especially at risk. Back-to-back infections, which are particularly common in winter months, can frequently result in a chronic cough. Similarly, coinfection with more than one of these organisms can occur, and this can increase the period of paroxysmal coughing. Prolonged cough after Chlamydyphila and Mycoplasma infections may also be quite common. A duration of cough of > 21 days in young children following pneumonia with these organisms has been found in 57% and 28% of patients, respectively.

Diagnosis

The diagnosis of postinfectious cough is clinical and one of exclusion. A careful medical history, including knowledge of the medical history of contacts, and sometimes the physical examination may provide clues to the diagnosis. As the cough is usually self-limited, it will resolve in time. When *M. pneumoniae* infection is suspected, as in school-age children or young adults, particularly in military personnel, in late summer or fall, acute and convalescent-specific serologic studies may help to confirm the diagnosis.

Recommendation

3. In children and adult patients with cough following an acute respiratory tract infection, if cough has persisted for > 8 weeks, consider diagnoses other than postinfectious cough. Quality of evidence, low; net benefit, intermediate; strength of recommendation, C

Treatment

The postinfectious cough is self-limited and will usually resolve in time. Therapy with antibiotics has no role in the treatment of postinfectious cough, as there is no evidence that bacterial infection plays a role. Based on the speculation that the postinfectious cough is due to inflammation, some authors in uncontrolled studies have successfully treated the cough with a brief course of corticosteroids starting with 30 to 40 mg of prednisone (or equivalent) in the morning, tapering to zero over 2 to 3 weeks. This regimen may be tried in those patients whose coughs become protracted and persistently troublesome. The organisms that are associated with postinfectious cough cause considerable transmigration of neutrophils across bronchial epithelial cells, and sputum analysis may show an increase in lymphocytes followed by an increase in neutrophils. *M. pneumoniae* causes intense airway neutrophil inflammation and bronchial hyperresponsiveness in animal models, and both can be suppressed by inhaled fluticasone propionate. Clinical data to support this approach in humans are lacking. In one small controlled trial, ipratropium bromide was shown to attenuate postinfectious cough. There have been no clinical trials conducted on the effect of centrally acting antitussive agents on postinfectious cough. Failure to respond to treatment should alert one to consider UACS due to rhinosinus diseases, asthma, or gastroesophageal reflux disease as the cause of the cough.

Recommendations

4. For adult patients with postinfectious cough, not due to bacterial sinusitis or early on in a *Bordetella pertussis* infection, while the optimal treatment is not known:

4a. Therapy with antibiotics has no role, as the cause is not bacterial infection. Level of evidence, expert opinion; net benefit, none; grade of evidence, I

4b. Consider a trial of inhaled ipratropium as it may attenuate the cough. Level of evidence, fair; net benefit, intermediate; grade of evidence, B

4c. In patients with postinfectious cough,
when the cough adversely affects the patient’s quality of life and when cough persists despite use of inhaled ipratropium, consider the use of inhaled corticosteroids. Level of evidence, expert opinion; net benefit, intermediate; grade of evidence, E/B

4d. For severe paroxysms of postinfectious cough, consider prescribing 30 to 40 mg of prednisone per day for a short, finite period of time when other common causes of cough (eg, UACS due to rhinosinus diseases, asthma, or gastroesophageal reflux disease) have been ruled out. Level of evidence, low; net benefit, intermediate; grade of evidence, C

4e. Central acting antitussive agents such as codeine and dextromethorphan should be considered when other measures fail. Level of evidence, expert opinion; net benefit, intermediate; grade of evidence, E/B

**B pertussis Infection and Cough**

One type of postinfectious cough that is particularly virulent is that caused by *B pertussis* infection. Recommendations for this section of the review relating to Bordetella infection and cough were made using data obtained from a National Library of Medicine (PubMed) search dating back to 1950, which was performed in August 2004, of the literature published in the English language. The search was limited to human studies, using the search terms “cough,” “Bordetella pertussis,” “Pertussis infection,” and “whooping cough.”

**Prevalence**

*B pertussis* is a small pleomorphic Gram-negative coccobacillus that has been increasingly recognized as a cause of persistent cough in adolescents and adults. Because it leads to severe paroxysms of coughing with frequent complications, is highly contagious in children and adults, and responds to appropriate antibiotic coverage when administered early in the course of the disease, it is considered separately from other causes of postinfectious cough. The organisms are inhaled into the respiratory system by aerosol droplets, where they adhere to and invade the ciliated epithelial cells. Unlike other causes of postinfectious cough, pertussis infection or whooping cough can result in prolonged episodes of coughing. In fact, postinfectious cough has been nicknamed the *hundred day cough*. The organism is highly contagious as one active case can infect 70 to 100% of household contacts and 50 to 50% of school contacts. The incidence of pertussis infection, or whooping cough, declined dramatically after the introduction of the whole-cell pertussis vaccine in the 1940s. Since the early 1980s, despite widespread vaccination, there has been an increase in incidence over all age groups, because complete immunization is not protective for all children, many children are incompletely immunized, and immunity wanes in most cases. The increase in incidence, however, has been particularly evident in adolescents and adults, with the greatest increase occurring in patients between the ages of 10 and 19 years. This likely occurs because immunity from immunization wanes in the decade that follows the most recent immunization and also because the number of adults who had immunity from natural infection in the prevaccine era is progressively decreasing. The annual incidence rate still remains highest among infants < 1 year of age, and in the majority of such children adults are the source of infection. Bordetella parapertussis has been shown to cause a disease similar to whooping cough but of shorter duration, possibly because it does not produce the pertussis toxin (PT), the principle agent responsible for severe coughing. Immunization with standard pertussis vaccines has not provided protection from *B parapertussis*, while modest protection has been seen with the newer acellular vaccines.

**Clinical Presentation**

Pertussis infection can present in a variety of settings; it may be an important cause of cough in college students, in military personnel, in referrals to a pulmonary specialist, in patients seeking emergency department care, in those seen in the primary care setting, in health-care workers, and in the elderly. Unfortunately, pertussis is not considered in the differential diagnosis of chronic cough by many practitioners. However, in a Canadian multicenter prospective study, pertussis infection was confirmed in 19.9% of adolescents and adults who met the criteria for postinfectious cough. The classic case of pertussis has been well-described. After an incubation period of 1 to 3 weeks, a 2-week virus-like illness ensues, and during this catarrhal phase symptoms of conjunctivitis, rhinorrhea, fever, malaise, and, later, cough occur. Leukocytosis and lymphocytosis, which are thought to be typical of a pertussis infection, are frequently not seen. The next phase, the paroxysmal phase, is characterized by worsening cough, often with the characteristic whooping sound, which consists of a series of expiratory bursts followed by a sudden loud inspiratory sound. In children < 2 years of age, vomiting or apnea is more commonly seen than the typical whooping sound. Adults may complain of shortness of breath and a tingling sensation in the throat, and
posttussive emesis is common. The whooping sound is also usually absent in adults. The cough tends to be spasmodic, and occurs more frequently at night and after exposure to cold air; it lasts usually 4 to 6 weeks but can persist for much longer during the convalescent phase. The duration and frequency of symptoms vary widely but are more severe in females and in nonimmunized individuals. In adults and adolescents, it is common to have a nondistinct protracted cough as the only manifestation of pertussis infection. And many individuals never become symptomatic. Clinical and serologic surveys of elderly subjects living independently have shown that between 3.3% and 8% have pertussis infections each year; yet, only 37.5 to 50% of such individuals are symptomatic.

**Diagnosis**

Both probable and confirmed cases of pertussis infection should be reported to the public health authorities. A clinical case is defined as an acute illness with a cough that is persistent for > 2 weeks and is associated with posttussive vomiting, the typical whooping sound, or severe paroxysms. A confirmed case is one in which *B. pertussis* has been isolated or is a clinical case that has been confirmed by polymerase chain reaction (PCR) or epidemiologic linkage to a confirmed case. A probable case meets the clinical case definition without laboratory or epidemiologic confirmation. The most reliable way to make the diagnosis is by detection of the organism from nasopharynx secretions. However, cultivating the organism requires enriched media, and its sensitivity has been reported to be as low as 25 to 50%. PCR is a rapid and highly specific test for *Bordetella* spp and has a sensitivity as high as 80 to 100%. Although widely used in the United States, PCR assays have not been standardized. A number of serologic studies are available, including IgG and IgA titers of the antibody to PT, filamentous hemagglutinin (FHA), pertactin, and fimbriae. The most generally accepted serologic criterion for diagnosis is the enzyme-linked immunosorbent assay test to demonstrate a significant increase in IgG serum antibody against PT. Paired sera are necessary as nonrising titers may represent past infection or previous immunization. The first serum sample should be taken within 2 weeks of the onset of cough, and the second should be taken 3 to 4 weeks later. The reported specificities and sensitivities of this test are 99% and 63%, respectively, when used for documenting community outbreaks of pertussis infection. Although widely used in epidemiologic surveys, paired sera titers have shown less usefulness in the clinical evaluation of cough because patients often delay seeking medical care and paired samples cannot be obtained. While a single serum specimen that shows high titers when compared to reference values is highly suggestive of a recent pertussis infection when there is a compatible clinical picture, no serologic method for diagnosis has been validated and approved for diagnostic use in the United States.

**Recommendations**

5. When a patient has a cough lasting for ≥ 2 weeks without another apparent cause and it is accompanied by paroxysms of coughing, posttussive vomiting, and/or an inspiratory whooping sound, the diagnosis of a *B. pertussis* infection should be made unless another diagnosis is proven. Level of evidence, low; net benefit, substantial; grade of evidence, B

6a. For all patients who are suspected of having whooping cough, to make a definitive diagnosis order a nasopharyngeal aspirate or polymer (Dacron; INVISTA; Wichita, KS) swab of the nasopharynx for culture to confirm the presence of *B. pertussis*. Isolation of the bacteria is the only certain way to make the diagnosis. Level of evidence, low; net benefit, substantial; grade of evidence, B

6b. PCR confirmation is available but is not recommended as there is no universally accepted, validated technique for routine clinical testing. Level of evidence, low; net benefit, conflicting; grade of evidence, I

7. In patients with suspected pertussis infection, to make a presumptive diagnosis of this infection, order paired acute and convalescent sera in a reference laboratory. A fourfold increase in IgG or IgA antibodies to PT or FHA is consistent with the presence of a recent *B. pertussis* infection. Level of evidence, low; net benefit, intermediate; grade of evidence, C

8. A confirmed diagnosis of pertussis infection should be made when a patient with cough has *B. pertussis* isolated from a nasopharyngeal culture or has a compatible clinical picture with an epidemiologic linkage to a confirmed case. Level of evidence, low; net benefit, substantial; grade of evidence, B

**Treatment**

In the case of proven or presumed pertussis infection, prospective clinical trials have shown that treatment with erythromycin (or trimethoprim/sulfamethoxazole when a macrolide cannot be given) is necessary; the recommended dose is 40 to 50 mg/kg/d in children and 1 to 2 g per day in adults for 2
weeks. Therapy should begin as soon as the disease is suspected and should not be delayed until confirmation of the diagnosis, as early therapy during the catarrhal phase (ie, the first 2 weeks) will rapidly clear B pertussis from the nasopharynx and decrease the coughing paroxysms and other complications. Patients with active cases should be isolated at home and away from work or school for 5 days after therapy with antibiotics is started. There is some evidence that therapy given in the paroxysmal phase may be effective, but it is usually of limited benefit. Erythromycin resistance has been reported but is quite rare (≤ 1%). Newer macrolides such as clarithromycin and azithromycin are also active against B pertussis and have a better side-effect profile. Until the past few years, only small clinical trials have been available to support their use. In a large multicenter randomized trial, azithromycin was found to be as effective as erythromycin estolate in the treatment of pertussis in children with much better compliance because of a better side-effect profile. The newer fluoroquinolones also show good in vitro activities against B pertussis, but there are no clinical trials to support their use. Prophylaxis for exposed persons has been found to be effective in decreasing the severity and transmission of the disease to others if therapy is begun early (ie, within the first 2 weeks of the infection).

The benefits of adding long-acting β-agonists, antihistamines, corticosteroids, and pertussis Ig have been studied in pertussis infection. No significant benefit has been found with any of these interventions in controlling the paroxysms of coughing. Results of trials in adults and children using acellular pertussis vaccines rather than whole cell vaccines suggest that in the future, pertussis may be safely and effectively prevented in all age groups. In the past pertussis vaccines have been approved only for children under age seven and a series of 5 doses (coupled with diphtheria and tetanus toxoid) is recommended before the 7th birthday. Acellular vaccines are currently approved for children in this age group. Two adult formulations of the new acellular vaccine are now licensed in North America (2005 approval in the US) and are combined with diphtheria and tetanus toxoid (dTap). The rapid rise in the number and proportion of cases of pertussis among adolescents and adults in recent years called for a study in this age group. A large multicentered randomized, controlled, double-blind trial of acellular pertussis vaccine in a population aged 15–65 years was funded by the National Institute of Allergy and Infectious Diseases and reported in 2005. The vaccine was highly effective, with a protection rate of 92% (95% confidence interval, 32–99%), and proved to be very safe in this age group. Because the rate of pertussis in the nonimmunized population in this study was 370 cases per 100,000, the potential for case rate reduction is enormous. In 2005, the US Advisory committee on Immunization Practices endorsed the use of a single dose of DTap vaccine in adolescents aged 11–18 years (www.cdc.gov/nip/pr/pr_tdap_jun2005.htm). A similar recommendation has just been announced for adults up to 65 years of age.

**Recommendations**

9. Children and adult patients with confirmed or probable whooping cough should receive a macrolide antibiotic and should be isolated for 5 days from the start of treatment because early treatment within the first few weeks will diminish the coughing paroxysms and prevent spread of the disease; treatment beyond this period may be offered but it is unlikely the patient will respond. Level of evidence, good; net benefit, substantial; grade of evidence, A

10. Long-acting β-agonists, antihistamines, corticosteroids, and pertussis Ig should not be offered to patients with whooping cough because there is no evidence that they benefit these patients. Level of evidence, good; net benefit, none; grade of evidence, D

11. All children should receive prevention against pertussis infection as part of a complete diphtheria, tetanus, acellular pertussis (DTap) primary vaccination series. This should be followed by a single dose DTap booster vaccination early in adolescence. Level of evidence, good; net benefit, substantial; grade of evidence, A

12. For all adults up to the age of 65, vaccination with the stronger formulation of DTap vaccine should be administered according to CDC guidelines. Level of evidence, expert opinion; net benefit, substantial; grade of evidence, E/A

**Summary of Recommendations**

1. When a patient complains of cough that has been present following symptoms of an acute respiratory infection for at least 3 weeks, but not more than 8 weeks, consider a diagnosis of postinfectious cough. Quality of evidence, expert opinion; net benefit, intermediate; strength of recommendation, E/B

2. In patients with subacute postinfectious cough, because there are multiple...
pathogenetic factors that may contribute to
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4. For adult patients with postinfectious
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on in a Bordetella pertussis infection, while
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4b. Consider a trial of inhaled ipratro-
pium as it may attenuate the cough. Level of
evidence, fair; net benefit, intermediate; grade
of evidence, B

4c. In patients with postinfectious cough,
when the cough adversely affects the pa-
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consider the use of inhaled corticosteroids.
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7. In patients with suspected pertussis
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12. For all adults up to the age of 65, vaccination with the stronger formulation of TDap vaccine should be administered according to CDC guidelines. Level of evidence, expert opinion; net benefit, substantial; grade of evidence, E/A

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